Notice of Allowability	Application No.	Applicant(s)	
	10/734,957	WATKINS ET AL.	
	Examiner	Art Unit	
	Jeffrey Stucker	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the preliminary amendment filed 02 May 2005*.

2. ☒ The allowed claim(s) is/are *41-49*.

3. ☐ The drawings filed on _____ are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date 9/16/04
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

PD

This Notice of Allowability is in response to the Preliminary Amendment filed 02 May 2005. Claims 41-49 are pending and allowable.

The following is an Examiner's Statement of Reasons for Allowance:

The closest prior art is JP 61-132869 which was applied in the parent application. However, this reference does not anticipate the claims as amended for the reasons given in the parent application, 09/905338, now US patent 6,872,578. The independent claim in this Application, claim 1, has been amended to read, in part, as follows:

> "...the second solid phase comprises microparticles of magnetically responsive material, the sizes of said microparticles varying in size over a range that is an aggregate of a plurality of subranges, each subrange distinguishable from other subranges of said aggregate by flow cytometry and by the immunological binding member coupled thereto, said microparticles being suitable for use in a multiplex assay procedure that includes the use of flow cytometry...."

The method thus requires a plurality of reagents, each for a different analyte, coupled to a plurality of magnetically responsive particles of varying size subranges, with each size subrange distinguishable from the others by flow cytometry and

by the coupled binding species, the microparticles being suitable for use in a multiplex assay procedure that includes the use of flow cytometry.

The reference overall discloses various techniques for separating bound (B) and unbound or free (F) antibodies. The first embodiment is found at the bottom of page 5 of the reference (English translation). In this embodiment mixed carriers are used, in which antigens are bound to latex particles having different particle sizes. B-F separation is then carried out, and concentrations of a plurality of analytes can be ascertained from the fluorescence intensities.

Magnetized latex particles are used in another embodiment of the process, which is described at the top of page 6. Here only a single antibody is analyzed for, and the magnetic particles are used to separate bound antibody from the unbound antibody by use of an electromagnet. This is a typical magnetic separation process. The two embodiments involve different techniques and processes. While both are included under the general topic of techniques for separating bound from free antibody in this reference, they are described as alternative processes and are not intended to be used in combination.

The presently claimed method requires particles that are for use in a process that requires re-suspension of the

particles after the magnetic field has been applied and the use of flow cytometry on the resuspended particles. Flow cytometry is a process that is sensitive to the composition of the particles and their interactions with each other. Adding a magnetic character to the particles can give the particles a strong interparticle attraction or repulsion (both of which can affect their ability to be resuspended). Adding a magnetically responsive component to the particle mass can seriously affect the properties of the particles. In the context of the present invention, magnetically responsive particles must do much more than simply offer a means to separate the particles from a liquid, or separate bound from free antibody, by placing a magnet nearby.

The problems and risks that arise when resuspension and flow cytometry are applied to magnetic particles in a multiplex assay system, are neither recognized nor addressed in the prior art, including JP 61-132869. Specifically:

None of the prior art on either flow cytometry or magnetized particles addresses the risk that magnetized particles will settle out before passing through the flow cytometry cell. Note that this risk is much greater with magnetic particles than it is with particles of latex, which is the traditional particle material used in flow cytometry.

None of the prior art on either flow cytometry or magnetized particles addresses the risk that magnetized particles upon resuspension will not completely separate and instead remain as aggregates that will clog the flow cell. Latex particles, such as are used in Coulter (GB patent 1,561,042, discussed below), or in the first embodiment of JP 61-132869, which have much less a tendency to form aggregates, do not present this problem, nor do they present a risk of comparable magnitude.

None of the prior art on either flow cytometry or magnetized particles addresses the risk of losing magnetic character of having magnetic characters of widely varying magnitude that would interfere with the particles' ability to function uniformly as magnetic particles, when the particles are fabricated in different sizes or with different dyes or some other differentiation parameter.

The combination of the two techniques is similar in nature to a rejection earlier in the prosecution of the parent application, namely that over the combination of Bibette et al. (US patent 5,245,964, which disclosed magnetic particles but not for use in multiplex assays) with the British patent of Coulter et al. (GB patent 1,561,042, which disclosed multiplex assays that did not use magnetic particles). It may appear that it

would be obvious to combine the two disclosures to provide a multiplex process using magnetic particles would be obvious, particularly since both references relate to particles having size subranges. However, to simply combine the teachings of the two references overlooks the above-mentioned complexities of seeking to adapt magnetic particles to a multiplex assay that includes flow cytometry. Additionally, each reference defines a complete process in and of itself, with no indication therein to suggest any such combination. From their disclosures, those skilled in the art would not be motivated to combine the two references. In addition, with the complexities mentioned above, those skilled in the art would not be taught from the references how to obtain a composition containing magnetic particles that are differentiable for use in a multiplex assay that includes flow cytometry.

JP 61-132869 does not provide any assistance in dealing with these potential problems. The two embodiments cited previously in this Office Action involve different techniques, and information about one is not necessarily combinable with information about the other. In particular, it would not be obvious to combine the teaching of the second embodiment to use magnetic particles with that of the first embodiment, a

multiplex determination that does not use, or need to use, magnetic particles.

Thus, the prior art does not anticipate or render obvious the claimed invention.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Papers related this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).

The Group 1600 Official Fax number is: (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Stucker whose telephone number is (571)-272-0911. The examiner can normally be reached Monday to Thursday from 7:00am-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (571)-272-0902.

JEFFREY STUCKER
PRIMARY EXAMINER